510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:

k043386

B. Purpose for Submission:

New assay and calibrators. Changes to calibrator verifiers.

C. Measurand:

Vancomycin

D. Type of Test:

Quantitative homogeneous enzyme immunoassay

E. Applicant:

Ortho-Clinical Diagnostics Inc.

F. Proprietary and Established Names:

VITROS Chemistry Products Vancomycin (VANC) Reagent, Calibrator Kit 11, TDM Performance Verifier I, II and III.

G. Regulatory Information:

1. Regulation section:
   Vancomycin Test System (21CFR862.3950)
   Assayed controls (21 CFR 862.3280)
   Calibrators (21 CFR 862.3200)

2. Classification:

   Class II

3. Product code:

   91LEH, 91DLJ, 91DIF

4. Panel:

91, Toxicology

H. Intended Use:

1. Intended use(s): See indications for use below.

2. Indication(s) for use:
   For *in vitro* diagnostic use only. VITROS Chemistry Products VANC Reagent is used on the VITROS FS 5,1 Chemistry System to quantitatively measure vancomycin (VANC) concentration in human serum and plasma. Serum or plasma vancomycin measurements are used in the diagnosis and treatment of vancomycin overdose and in monitoring levels of vancomycin to help ensure appropriate therapy.

   For *in vitro* diagnostic use only. VITROS Chemistry Products Calibrator Kit 14 is used to calibrate VITROS 5,1 FS Chemistry Systems for the quantitative measurement of vancomycin (VANC).

   For *in vitro* diagnostic use only. VITROS TDM Performance Verifier is an assayed control used to monitor performance of ACET, CRBM, DGXN, PHBR, PHYT, and VANC on VITROS Chemistry Systems.

3. Special conditions for use statement(s):
   The assay is for use with serum and EDTA plasma. It should not be used with other anticoagulants.
4. Special instrument requirements:
   For use on the VITROS 5,1 FS Chemistry System

I. Device Description:

Reagent 1 contains vancomycin labeled with glucose-6-phosphate dehydrogenase and other non-reactive components. Reagent 2 contains NAD, glucose-6-phosphate, murine monoclonal antibodies reactive to vancomycin, and other non-reactive components.

Calibrator Kit 11 is an aqueous solution containing vancomycin, buffer, proteins, salts, surfactants and preservatives. Nominal values of vancomycin (ug/mL): 0, 5, 10, 20, 30, 50.

The performance verifiers are assayed controls prepared from bovine serum to which therapeutic drugs, salts and preservatives are added.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Syva® EMIT® 2000 Vancomycin Assay and calibrators. VITROS Chemistry Products Performance Verifiers.

2. Predicate 510(k) number(s):

   k020692 (reagents), k020845 (calibrators), k042476 (performance verifiers)

3. Comparison with predicate:

   The devices are similar in intended use and methodology. Both devices are homogeneous enzyme immunoassays. The predicate device is for use on Syva Analyzer Systems; the new device is for use on the VITROS 5,1 FS Chemistry System.

   The VITROS Chemistry Products TDM Performance Verifiers are substantially equivalent to VITROS Chemistry Products TDM Performance Verifiers, currently in commercial distribution (K042476). Vancomycin has been added and labeling updated to add assigned values.

K. Standard/Guidance Document Referenced (if applicable):

NCCLS Guideline – EP5-A, Evaluation of Precision Performance of Clinical Chemistry Devices

NCCLS Guideline – EP6-A, Evaluation of the Linearity of Quantitative Analytical Methods

NCCLS Guideline – EP7-A, Interference Testing in Clinical Chemistry

NCCLS Guideline – EP9-A2, Method Comparison and Bias Estimation Using Patient Samples

L. Test Principle:

Patient sample is added to reagent 1, which contains vancomycin labeled with glucose-6-phosphate dehydrogenase, followed by reagent 2, which contains antibody reactive to vancomycin, glucose-6-phosphate and NAD. The assay is based on competition between vancomycin in the sample and labeled vancomycin. The concentration of vancomycin in a sample is measured in terms of enzyme activity and can be monitored spectrophotometrically at 340 nm. Unknown sample concentrations are determined using the (stored) calibration curve.

M. Performance Characteristics (if/when applicable):

Analytical studies and method comparison were performed with 3 lots, at the manufacturer's site.

1. Analytical performance:

a. Precision/Reproducibility:

Within-day and within laboratory precision was determined using the system's bovine serum-based QC materials. The evaluation followed NCCLS EP-5A, with 2 replicates per run, two runs per day for 22 days, n=88 observations. Within-day runs were separated by at least 2 hours. Calibration was performed once each week. The sample order was randomized. Results for within-day and within-lab are shown. Testing of multiple lots and instruments yielded similar results.

Sample	Mean (ug/mL)	N	Within-day SD (ug/mL)	Within-lab (ug/mL)	Within-lab %CV
Control level 1	7.37	88	0.231	0.449	6.1
Control level 2	21.84	88	0.598	1.108	5.1
Control level 3	35.46	88	1.054	2.048	5.8

Within-run precision was also estimated for patient serum pools at concentrations near and around 5.0 ug/mL. Standard deviations were calculated based on 5 replicates, for each of 3 reagent lots, at each vancomycin level (i.e. total of 15 observations at each level). Results were all within the within-run standard deviation limits of 0.22 ug/mL.

b. Linearity/assay reportable range:

Serum pools with vancomycin concentrations at 14 levels spanning the linear range were evaluated. Each level was tested in replicates of 5 and average values of observed/expected concentrations were determined. The evaluation was performed according to NCCLS EP-6A and supports the assay reportable range, 5.0-50 ug/mL. In this range deviations from expected concentrations were within bias limits of approximately +/-0.6 ug/mL at the low end, and approximately +/-4.9 ug/mL near the high end, of the reportable range.

Recovery after sample dilution with the recommended diluent was also evaluated. Serum samples with vancomycin concentrations in the range of approximately 31-49 ug/mL were diluted 2x and 4x. Mean recoveries (of triplicates) were all within acceptance criteria of 90-110%.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
VITROS Chemistry Products Calibrator Kit 11, and performance verifiers I, II and III are for use with this device.

Value assignment for calibrators: Values assigned to calibrators are traceable to USP vancomycin reference standard. Concentrations of stock solution, prepared gravimetrically, are confirmed by GCMS or HPLC methods. Expanded uncertainties for product calibrators (the 95% confidence interval around the assigned value mean) are calculated as 0.53 for 5 ug/mL and 2.44 for 50 ug/mL. Correlation analyses (described in the 510(k)) to confirm that trueness is transferred indicate slopes and intercepts approaching 1 and 0, respectively, and correlation coefficients > 0.99.

Calibrator long-term stability: Calibrators tested are stored at 9 degrees C and evaluated at intervals up to and past the expiration date. Testing compares results of samples using calibration with the test calibrators to those obtained with reference calibrators on the Syva 30R Analyzer. The samples used in testing were sample pools at medical decision points, with minimum of 20 replicates at each decision point. Acceptance criteria for bias are:
+/- 0.405 ug/mL for vancomycin concentrations < 6 ug/mL, and
+/-0.0607[vancomycin] + 0.0405 ug/mL for concentrations > 6 ug/mL.

Calibrator opened-bottle stability: Opened bottle stability is evaluated by testing and re-storing bottles at 2-8 degrees C, at intervals up to, and past, the expiration date. Bias is determined, relative to unopened calibrators. Limits are:
+/- 0.165 ug/mL for vancomycin concentrations < 6 ug/mL, and
+/-0.0247[vancomycin] + 0.0165 ug/mL for concentrations > 6 ug/mL.

Value assignment for calibrator verifiers: Performance verifier lots are tested with each reagent to establish target values. Allowable ranges applied reflect estimates of expected lab to lab variability. The range of means is calculated from precision data from multiple systems (minimum 5) in multiple laboratories. A pooled SD is determined based on total SD's from each site and the range is calculated based on 3x pooled SD. The range of means for controls are provided on performance verifier assay sheets.

Verifier stability: Long-term stability for controls is evaluated using vials stored at -18 degrees C. Opened stability is evaluated using vials opened and stored at 2-8 degrees C up to 7 days. Observed concentrations (mean of replicates) are compared to those at "time 0", at intervals up to and past expiration. Acceptance criteria, in terms of bias relative to time 0, are shown:

	Long-term acceptance limit (ug/mL) (+/-)	Opened vial acceptance limit (ug/mL) (+/-)
Level 1 7.5 ug/mL	2.16	0.7
Level 2 23 ug/mL	6.52	2.06
Level 3 40 ug/mL	11.3	3.56

d. Detection limit:

The limit of detection, 5.0 ug/mL, is based on evaluations with vancomycin-negative serum samples from 10 human donors, as well as from low level calibrator material. Three reagent lots, 2 calibrator kit lots and 2 instrument systems, were used in testing and multiple determinations. The lower limit of detection was calculated as:

$3.3X\sqrt{\text{Calibration Error Variance (SD)}^2 + \text{Pooled replicate Variance (SD)}^2}$

Results based on these calculations support the detection limit of 5.0 ug/mL.

The bias limit for linearity for concentrations < 6 ug/ml vancomycin is +/- 0.63 ug/mL. In addition, within-run standard deviations for samples containing vancomycin levels near the limit of detection was +/-0.22 ug/mL (see Precision, above).

e. Analytical specificity:

Testing followed EP-7A for the paired-difference method. Four determinations were made for each substance using two reagent lots. Bias was calculated as the mean vancomycin concentration of the test substance pool minus the mean concentration of the control pool.
Endogenous compound tested, and results are shown:

Compound and concentration tested	Concentration vancomycin	Bias detected
Bilirubin 60 mg/dL	11 ug/mL vancomycin	No bias detected, <1.1
Bilirubin 60 mg/dL	46 ug/mL vancomycin	No bias detected, < 4.4 ug/mL
Intralipid 1000 mg/dL *	28 ug/mL vancomycin	No bias detected, < 2.7 ug/mL
Hemoglobin 1000 mg/dL	28 ug/mL vancomycin	Negative bias of approximately - 3.25 ug/mL

* Intralipid concentrations of 600 mg/dL and higher caused an analyzer condition code and suppressed results. When these samples were diluted 1:4 with saline, sample results passed acceptance limits.

A serum pool containing approximately 20 ug/mL vancomycin was used to test for interference with other commonly co-administered drugs. The drugs and concentrations tested are listed in the product package insert. Acceptance criteria are bias < 2.1 ug/mL. None of the drugs tested interfered under the conditions tested.

f. Assay cut-off:

NA. This is a quantitative assay.

2. Comparison studies:

a. Method comparison with predicate device:

One hundred and two human serum samples were evaluated with the VITROS Chemistry Products Vancomycin Reagent and the Syva EMIT® Vancomycin Plus. Samples were selected to be patient serum samples of 2 mL or more that contained vancomycin across the reportable range of the assay. Each sample was measured in triplicate. The analysis was also performed using singlicates and results of this analysis are shown below. Similar results were obtained for 3 lots tested. Slope = 1.01, intercept = 0.02 ug/mL, r= 0.995, sy/x = =1.21.

b. Matrix comparison:

Serum and plasma EDTA samples were evaluated by paired difference testing of samples with concentrations across the reportable range. The bias between the mean values (n=3) was defined as: bias = test sample minus serum sample. Acceptance limits, in terms of bias, range from approximately 0.6 ug/mL for the low end of the range to approximately 4.8 ug/mL for the high end of the range.

Results support use of the assay with serum and EDTA plasma. The assay should not be used with other anticoagulants.

3. Clinical studies:

a. Clinical Sensitivity:

N/A. (Not typically reviewed for this type of test)

b. *Clinical specificity:*

N/A. (Not typically reviewed for this type of test)

c. *Other clinical supportive data (when a. and b. are not applicable):*

4. Clinical cut-off**:**

   N/A. See expected values

5. Expected values/Reference range:

   A discussion of reference ranges from the literature is provided.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.